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07/893,610 06/03/92 MORRISON

S. BD1-CIP-EWCI
EXAMINER

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NISBET, T

ART UNIT

PAPER NUMBER

1846
DATE MAILED:

03/23/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 1/27/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned: 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 39-54 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 39-54 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

III. DETAILED ACTION

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. Claims 39-54 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited DNA constructs for expression of a chimeric polypeptide which is a subunit of an immunoglobulin molecule. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Since applicants have not submitted any significant rebuttal in papers 15 or 16, rejections are maintained for reasons of record as stated in papers 5, 7, and 10, mailed November 29, 1988, May 24, 1989, and September 25, 1990, respectively.

In addition, the following rejection is made. The enablement rejection is necessitated by the evidence submitted in the 131 affidavit. The affidavit submits essentially 4 separate experiments in which antibody binding was obtained. Of these experiments, only the last, performed in paragraph 18 was successful. In fact, this experiment was only successful when a particular phosphate buffer was used. Therefore, in view of a showing that only 1 in 4 of the experiments are operative in the instant claims, the instant invention cannot be considered to be enabled for any and all non-producing cell lines.

Furthermore, undue experimentation would be required to practice the instant invention in view of the fact that the J558L cell line underwent some unexplained mutation (see paragraph 18, lines 3 and following) which resulted the single chain loss mutant becoming a double chain loss mutant. Therefore, there is a reasonable likelihood that the expression of antibodies was a peculiarity of the mutation of the TAO 6 or 18 cell lines of the instant 131. Otherwise, the other cell lines would have worked also. Alternatively, the phosphate buffer may have been the reason no binding was obtained with the original TAO cell lines since alteration of the buffer is the element that resulted in the success of the last experiment. In short, the record is not completely clear as a result of the affidavit which was submitted to swear behind the Ochi reference of record. Therefore, applicants are invited to submit evidence which might clarify the aforementioned inconsistencies and enable the scope of the instant claims.

17. Claims 39-48 and 52-54 are rejected under 35 U.S.C. § 103 as being unpatentable over Cabilly (L,R, or 2A) or Boss (2b) in view of Gillies(S).

Applicant's arguments filed May 23, 1991 and March 25, 1991 have been fully considered but they are not deemed to be persuasive.

Rejections are maintained for reasons of record, stated in papers 5, 7, and 10, mailed November 29, 1988, May 24, 1989, and September 25, 1990.

Applicant's arguments as set forth in paper 16, filed May 20, 1991, may be summarized as follows. Applicants argue that the prior art involving immunoglobulin production in mammalian cells does not demonstrate the certainty of functionally producing immunoglobulins where both immunoglobulin chains are exogenous to the host cell. Further traversal is made with respect to the inadequacy of the Cabilly references. Cabilly is alleged to be inadequate in several areas. First, applicants emphasize that the instant receptors are functionally produced and assembled in the host cell rather than reconstructed after the fact, as in Cabilly. Second, Cabilly fails to mention any of the attendant advantages of mammalian expression systems demonstrated by the instant invention. Third, the prior art shows that bacterial expression systems do not functionally assemble immunoglobulins. Finally, arguments are made comparing the lack of enablement of the Cabilly reference when compared with the instant specification. Final arguments deal with the removal of the Boss patent from the prior art as the publication date is after the filing of the first parent application.

As regards the possibility of producing two exogenous immunoglobulin genes in a cell which does not produce immunoglobulin, the argument is not persuasive because the Cabilly references provide just such a teaching. The teaching is, however, a bacterial teaching. Nonetheless, the prior art does indeed teach the production of two immunoglobulin chains which are exogenous to the host cell expression system. The only difference between the instant invention and the prior art is now the type of host cell.

The Gillies reference solves this problem. The Gillies reference fails to teach production of two exogenous immunoglobulin chains in a host system, but ample description and enablement is provided for the functional production of immunoglobulins in mammalian hosts. Given Cabilly's explicit suggestion of mammals, one of ordinary skill in the art would have had ample motivation to combine the teachings of the Cabilly reference with the attendant advantages known to result from mammalian cell expression.

In sum, the enablement of Gillies solves applicant's concern with the mere paper reference of Cabilly. Applicant's for enablement under §35 U.S.C. 112 are far more stringent than requirements for enablement under §35 U.S.C. 102/103. So, the law demands that applicant's specification be far more explicit than the prior art (In re Lukach, 169 USPQ 795; Chester v Miller, 15 USPQ2nd 1333).

Moreover, the elements of Cabilly which are lacking are in fact supplied by Gillies, therefore, the problems of functional assembly are solved as well as the attendant advantages of mammalian cell expression. Furthermore, applicants have provided evidence on pages 4 and 5 of paper No. 16, that immunoglobulin subunits were known to functionally assemble in mammalian expression systems. Therefore, the fact that one of skill in the art is specifically motivated by Cabilly to use mammalian systems and that mammalian systems were known to functionally express exogenous immunoglobulin, would render the instant invention obvious to one of ordinary skill in the art.

Finally, applicant's arguments concerning the date of the Boss reference are not considered persuasive because the claims at issue are not limited specifically to receptors that are not chimeric. Failure to specifically claim a broader embodiment is not equivalent to specifically excluding said broader embodiment. Therefore, the instant claims cannot be given the August 1984 priority because these claims read on material not disclosed in the original parent.

The arguments filed 1/27/92 with the two affidavits concerning the unpredictability of the instant yields are not persuasive because the rejection is maintained because no arguments have been presented which would establish why the unexpected yield of a single cell line would be predictive of all cell lines. The unpredictability of the art as delineated by applicants would certainly seem to support the undue nature of extrapolating the instant results to other cell lines. Essentially, the rejection is maintained because applicants have extremely broad claims to products disclosed in the prior art which applicants urge are patentable base on results of a single cell line. Applicants have not submitted arguments to buttress the statistical significance of their unexpected results. See Ex parte Gelles 22 USPQ 2nd 1318. Dr. Morrison's arguments in paragraph 10 of the 132 declaration of Paper No. 24, filed Jan. 24, 1992, are drawn to the discussion of the instant invention's distinctiveness over the prior art rather than the reasons for extrapolating the isolated unexpected results to all cell lines. Applicants are invited to clarify and

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Nisbet whose telephone number is (703) 308-1794. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David L. Lacey
DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
3/22/93